PATENT COOPERATION TREATY

Rec'd PCT/PTO 16 JUL 2004

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 18 MAY 2004
WIPO PCT

Applicant's or agent's file reference PC/DM/P12680PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/00187	International filing date *(day/month/year)* 16.01.2003	Priority date *(day/month/year)* 16.01.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/68		
Applicant UNIVERSITY COURT OF THE UNIVERSITY OF GLAS.. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.08.2003	17.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Aguilera, M Telephone No. +31 70 340-3897

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00187

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-81 as originally filed

Claims, Numbers

1-27 as originally filed

Drawings, Sheets

1-13 as originally filed

Sequence listing part of the description, pages:

1-2, filed with the letter of 23.03.2003,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 8, 14, 26, 27 (all complete); 1-7, 9-13 and 15-25 (all partially)

   because:

   ☒ the said international application, or the said claims Nos. 1, 3-10 and 15-21; in regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 8, 14, 26, 27 (all complete); 1-7, 9-13 and 15-25 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7, 9, 10, 15-23
	No:	Claims	11-13, 24 and 25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7, 9-13 and 15-25
Industrial applicability (IA)	Yes:	Claims	2, 11-13, 22-25
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion (Continuation)

1.1 It is understood that the diagnostic methods of claims 1 and 3-10, and the methods of treatment of claims 15-21 are to be performed in the bodies of donor and/or recipient, first, because this possibility is not explicitly excluded, and, second, because the limitations of dependent claims 2 and 22 to methods performed outside the bodies clearly imply so, and would otherwise be meaningless.

For the assessment of said methods on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Therefore, in accordance to the practise of the EPO as IPEA, no opinion with regard to industrial applicability will be given on present claims 1, 3-10 and 15-21 (Article 34(4)(a)(i) and Rule 67.1(iv) PCT).

1.2 For reasons of conciseness, Inventions 2-37 were listed in a single paragraph of the International Search Report, which refers to claims 8 and 14 as partially searched. However, said claims do not comprise any reference to the G22P1 protein, which is the subject of Invention 1 as explained in the ISR. Since the applicant chose not to pay additional search fees, only Invention 1 was searched, leaving the subject-matter of claims 8 and 14 completely out of the search. Therefore, claims 8 and 14, both complete, are not subject of this International Preliminary Examination Report because they were not subject of the International Search Report (Rule 66(e) PCT).

V. Reasoned statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: GB-A-2 321 642 (GERON CORP ;UNIV TECHNOLOGY CORP (US)) 5 August 1998
D2: US-B1-6 277 613 (SMITH SUSAN ET AL) 21 August 2001
D3: US-A-6 020 166 (BIANCHI ALESSANDRO ET AL) 1 February 2000
D4: US-A-5 939 270 (BOUTRY MARC ET AL) 17 August 1999
D5: MUNIYAPPA K ET AL: 'TELOMERE STRUCTURE, REPLICATION AND LENGTH MAINTENANCE' CRITICAL REVIEWS IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, CRC PRESS, BOCA RATON, FL, US, vol. 33, no. 4, 1998, pages 297-336, XP002938542 ISSN: 1040-9238

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 Reagents for determining the level of expression of a telomere binding protein, including PCR primers for the detection of mRNA, are known for virtually all telomere binding proteins whose sequence was known at the date of priority. D1, D2 and D3 are only three of the multitude of documents disclosing such reagents. The fact that they are to be used in a specific method does not confer them novelty, even if the method was novel.

2.2.2 D1 discloses a non-human mammalian tissue, from a transgenic animal, in which the expression of a telomere binding protein (telomerase reverse transcriptase subunit, TRT) has been enhanced (see pages 167-169). Similar disclosures can be found in the prior art for other telomere-binding proteins, for example Tankyrase and A-TRFs (see D2, column 35, and D3, column 34)

2.2.3 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 11-13, 24 and 25 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.3 INVENTIVE STEP (Art. 33(3) PCT)

2.3.1 Document D4 is considered to represent the most relevant state of the art and discloses a method of screening mammalian donor tissue for predisposition to rejection (see Abstract, column 3 and claim 1). The method comprises the step of determining the level of expression of an endogenous protein selected from a list of 25 proteins (see column 4 and claim 1), and comparing the determined level to a reference level present in a normal organ, wherein altered levels of expression is indicative of a predisposition to rejection (see column 3, lines 35-38).

2.3.2 The subject-matter of claim 1 differs in that the marker protein is chosen from the group of telomere binding proteins.

2.3.3 The problem to be solved by the subject matter of claim 1 may therefore be regarded as providing further marker proteins whose altered expression is indicative of predisposition to tissue rejection. The solution would be to use a telomere binding protein as a marker.

2.3.4 This solution cannot however be considered as involving an inventive step (Article 33(3) PCT) because it does not solve the technical problem posed. This IPEA finds extremely unlikely that indeed all the telomere binding proteins known at the date of filing provide for reliable prognostic markers of tissue rejection. The reasons therefor are explained below (see objections under Article 5 PCT).

2.3.5 Dependent claims 2-10 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step for the following reasons:

2.3.5.1 Claim 2 is considered implicit to the method of claim 1. Otherwise, the method of claim 1 is not susceptible of industrial applicability.

2.3.5.2 The features of claims 3, 4 and 7 do not limit the scope of the claimed method to a reasonable generalization from the disclosure, and therefore they bear the same defect as claim 1 in that the technical problem posed is not solved (see above).

2.3.5.3 Claims 5 and 6 recite merely two of several straightforward possibilities from

which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

2.3.5.4 The features of claims 9 and 10 fall under the scope of routine experimental design and optimization, and the skilled person would include these features in order to solve the problem posed without the involvement of an inventive step.

2.3.6 The same reasoning explained for claim 1 applies to the methods of claims 15-22, as long as they are performed outside the human or animal body (i.e. in isolated tissue or organs; see also above), and to use of claim 23, because such method and preparation do not appear to solve the technical problem posed.

2.3.7 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 1-7, 9-13 and 15-25 does not involve an inventive step (Rule 65(1)(2) PCT).

2.4 SUFFICIENCY OF DISCLOSURE (Art. 5 PCT)

2.4.1 The present application documents demonstrate that the mRNA expression of four specific telomere binding proteins (G22P1, XRCC5, hPOT1 and SIRT2) is altered in a specific tissue rejection case, kidneys which have undergone chronic allograft nephropathy (CAN) when compared to pre-transplanted tissue. However, the scope of the subject-matter claimed covers the prognosis of rejection of any tissue, from any mammalian donor, into any host irrespective of species, age and condition, by measuring the level of any telomere binding protein in the donor tissue. The discrepance between the claimed scope of protection and the actual contribution to the art is evidenced by the following:

2.4.1.1 The very different etiology of the multitude of tissue rejection reactions: different species within donor mammals, different donor tissues, different host reactions (acute, chronic,...).

2.4.1.2 The very different structural and functional properties of the telomere binding

proteins (see for example D5, pages 303-306): different effects on telomere stability (stabilization, destabilization); different telomere binding properties (dsDNA, ssDNA, different DNA sequences, other telomeric proteins); different activities alone and combined (enzymatic, recruitment, blocking,...), and the different patterns and timing of expression of the telomere binding proteins in different tissues and cell subpopulations. The fact that they bind to the telomeres at certain stages in certain cell types does not appear to provide a mechanistic link for all of them, irrespective of their structure and function, to be considered reliable markers of tissue rejection.

2.4.1.3 The fact that an altered mRNA expression does not necessarily mean a consequent alteration in the protein levels, because some factors like mRNA stability and turnover, and protein synthesis, stability and turnover may have an influence in the levels of telomerase binding protein measured.

2.4.1.4 The fact that alterations in the mRNA levels of four marker genes occur after the kidney has been transplanted and a CAN reaction has already taken place, as shown in the application. The present documents do not prove that kidneys in which the expression of said genes was altered before transplantation show a higher risk of developing CAN. Because such evidence is not provided, the reliability and reproducibility of the method, even if limited to the above mentioned 4 mentioned markers in the prognosis of CAN, is doubtful.

2.5 Considering these facts, this IPEA has reasonable doubts concerning first, the reproducibility of the invention as claimed, and second, the burden of experimentation and inventive skill necessary to carry out the invention over the whole claimed area. At present, the imbalance between the teaching of the present application and the scope of the claims is contrary to Article 6 PCT, because it renders the subject-matter claimed not sufficiently disclosed.